Roche

July 2, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0571; Draft Guidance for Industry on Drug Substance Chemistry, Manufacturing and Control Information; 69 Federal Register 929 (Jan 7, 2004)

Dear Sir/Madam:

This document contains consolidated comments submitted by Hoffmann-La Roche with regard to the subject draft guidance. While the comments include a 'line listing' of specific details (see Attachment), there are also a number of broader issues which Roche would hereby like to highlight.

Starting Materials:

The concept of a "significant non-pharmaceutical market" as a starting material criterion appears to lack a scientific basis and would seem to have very little, if any, bearing on 'risk.' There are many well characterized and commonly available starting materials which are produced only for the pharmaceutical sector, such as protected amino acids, functionalized sugars, functionalized purine bases, etc. There should be no difference in the assignment of these as opposed to those materials produced for, say, the foods sector. The categorization should be in terms of commercial vs. non-commercial materials. 'Commercial' should be defined as a product which is offered by a company for free sale, listed in its product catalogue, product marketing sheets, product definition brochure or other advertising media and which is available in quantities capable of supporting commercial pharmaceutical manufacturing.

The whole "Propinquity" concept requires reevaluation. It is overly restrictive and arbitrarily defined. It is not very important whether or not a starting material is separated from the final intermediate by several steps; the important aspect for the quality of a drug substance is how specific the process is with regard to minimizing impurities or how efficient the purification steps are with regard to elimination of impurities. This section serves no real purpose and should be replaced by a discussion focusing on efficiency of purification steps rather than number of steps which separates point A from point B.

The issue of "Carryover of Impurities" also needs to be reconsidered. The logic inherent in this section seems fundamentally flawed and contradicts current thinking regarding sound science and risk assessment. The issue must not be source and carryover of impurities – whether they are from starting materials or intermediates – but rather how those impurities, whether real or potential, are identified, qualified and controlled. Basically, Roche believes that this section should be eliminated.

2003D-0571

C17

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

The starting material restrictions based on 'complexity of structure' would appear to ignore three decades of advances in analytical chemistry. "Complex" is not defined and is a highly subjective term. Compared to methanol, cyclohexanol is "complex." Many 'complex' materials are very well characterized. For example, D-ribose with its four chiral centers might appear stereochemically complex, but is quite well characterized and could hardly be viewed as an inappropriate starting material. The emphasis must be placed on the degree of characterization, not on perceived complexity. Complex molecules with multiple functionality may be well characterized and controlled using analytical techniques which, at one time, were considered 'advanced techniques' e.g., NMR, MS, chiral HPLC. Today, these and other quite sophisticated techniques are commonplace. They are major factors in mitigating risk associated with the appropriate management of complex structures.

Description of the Manufacturing Process and Process Controls:

A basic concept in the description of the manufacturing process should be an avoidance of unnecessary detail which has little bearing on the control of API quality and thus on risk to the patient. Therefore, only detailed process controls which are considered to be 'critical' to the process should be included. Inherent in this is an adequate and rigorous definition of 'critical.' Inclusion of non-critical controls only adds to the regulatory burden of the sponsor and the reviewer with no added value. Furthermore, the description should focus on critical process parameters and critical controls and avoid steps themselves being labeled as critical.

Reprocessing:

Certain operations which industry might well consider reprocessing have not been clearly included in the guideline definitions. Particularly, several examples exist where there might be 'very low risk' reprocessing of APIs subsequent to QC release, for example, removal of extraneous foreign material or the blending of lot 'heels.' Defining these operations as reworking adds unjustifiable regulatory burden for the manufacturer.

Recovery:

The reuse of solvents which are not returned to virgin grade, but are appropriate for use, has long been a situation where the sponsor must hold the justification documentation at its site and available to inspection. Requiring that this information, which may well be developed post-approval, in the CMC section is a new requirement and will not only add to regulatory burden, but will result in sponsors not pursuing acceptable reuse and resulting in increased ecological burden.

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Hoffmann-La Roche
July 2, 2004

Retest Period Definition:

The assignment of a retest period must be based on sound scientific data, including release data, stability data, storage data, etc. The draft guidance definition of retest period allows for no retest period subsequent to the original retest period. Rather, a lot to be used in drug product manufacture after its original retest period must be retested each time and 'then used immediately.' Roche believes that this is contrary to longstanding industry practice (i.e. to assign subsequent retest periods) which has always been based on good science.

Roche hopes that the Agency will consider these comments as it works with industry to develop a guidance which meets the needs of manufactures and regulators, but which does so within the current climate of sound science and risk-based assessments.

Sincerely,

HOFFMANN-LA ROCHE INC.

David L Ridge

David Ridge, Ph.D.
Group Director
Drug Regulatory Affairs
Phone: (973) 562- 3696
Fax: (973) 562-3554

DR/sp
Attachment
HLR No. 2004-1720

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

ATTACHMENT

SCORECARD: Roche Comments on: Draft FDA Guidance "Drug Substance – CMC Information"

SCORECARD: Roche Comments on:
Draft FDA Guidance "Drug Substance – CMC Information"
(Docket No. 2003-0571)
January 2004

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
General			While the document claims not to provide specific guidance on biologicals or fermentation, there are repeated references through the document to these areas. Such references should be carefully excluded from this guidance	This guidance should focus on the defined scope and and separate guidance should focus on fermentation and on biologics	1
General			Numerous 'boxes' throughout the document providing citations to 'Additional guidance' are redundant and generally not useful	Guidance document should be as streamlined as possible, without 'clutter.'	3
248	II.D.2		physical properties critical to the applicant's product, such as solid state form ~~or particle size distribution~~	Particle size is not an inherent physical property (such as polymorphism). If particle size is relevant, it should be discussed under section 3.2.S.4, otherwise excluded	3
301	III.A.		abbreviations ~~or nicknames~~ used	Inappropriate and covered by 'abbreviations.'	3
377	IV.A.		manufacturing ~~responsibility~~ operation	The meaning of manufacturing 'responsibility' is ambiguous	3
383	IV.A.		~~Building numbers or other specific identifying information should be provided for multifacility campuses~~	This information is not currently required in an NDA/MF and is contradictory to BACPAC I	2

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
390-1	IV.A.		It is not necessary to list the name of a contact person for preapproval inspections in the application. Additionally, personnel changes would invalidate that listing. That activity is usually accomplished via personal contact of the site with the FDA District. Optionally, one could list a specific function and site phone number that could be contacted.		3
408	IV.B.1		Too much detail is requested in the Flow Diagram which is duplicated in the Narrative Description, e.g., solvents, auxiliary materials, critical controls, operating parameters and expected yield.	Duplicative and without value in the Flow Diagram	2
409-10	IV.B.1		The entire manufacturing process should be depicted (i.e., starting materials through **final** drug substance)	Testing is not relevant to understanding of the manufacturing process	2
414	IV.B.1		~~with identification of those steps that are critical~~	Duplicative and without value in the Flow Diagram	2
422	IV.B.1		postsynthesis materials' is not a common term and should be clarified here (at first use)	For clarification	3
423	IV.B.1		The value of molecular formulae and weights in a Flow Diagram is questionable.	This an opportunity to rid the section of information having no value.	3
427	IV.B.1		~~Operating parameters for each manufacturing step~~	This information is better suited to the narrative section	3
431	IV.B.1		~~Expected yield for each manufacturing step~~	This information is better suited to the narrative section	3

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
441	IV.B.2		manufacturing steps undertaken ~~and the scale of production should be provided~~	Scale is currently not required and changes in scale need not be reported	2
442	IV.B.2		The description should identify all critical process controls and the associated numeric ranges, limits, or acceptance criteria. ~~Furthermore, any process controls that are considered critical process controls should be highlighted.~~ See below for additional information on critical process controls.	Only critical process controls need be addressed in the NDA/DMF, not all process controls. Take this opportunity to streamline NDA requirements to cover only essential information. "Critical" must be further defined	1
454	IV.B.2		Type of equipment (~~e.g., Centrifuge) used,~~ including materials of construction) ~~when critical~~ if critical to control of material quality	Not all types of equipment are critical and should not have to be reported	1
456	IV.B.2		~~Identification of the manufacturing steps that are considered critical~~	Identification of 'critical steps' is considered to be irrelevant. What is important is identification of critical parameters	1
457	IV.B.2		All critical process controls and the associated numeric ranges, limits, or acceptance criteria ~~with critical process controls highlighted~~	Same as for line 442 above	1
462-7	IV.B.2		Identification of these steps is generally not known in advance of commercial manufacturing		3
466	IV.B.2		~~Identification of manufacturing steps that use recovered solvents . . .~~	If recovered solvents are returned to virgin condition, no reporting should be required	2
471	IV.B.2		~~Identification of processes that involve combining intermediate or drug substance batches . . .~~	Combining multiple batches of intermediates is a normal part of processing and should not require specific mention.	2
473	IV.B.2		Typical yield ~~ranges~~ (~~weight and~~ percent) for each manufacturing step	Scale and weight should not be required. Typical yield should be adequate	3

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
477	IV.B.2		References to biological starting materials seem inappropriate in light of the scope of this guidance	Keep guidance focused on the defined scope	2
488	IV.B.2		A statement should be provided that bovine-derived materials used or manipulated in the same facility comply with current requirements. ~~from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not~~	The list of BSE-free countries is rapidly growing smaller and if would seem that in the near future, the country list may not be the critical control, but other requirements will implemented.	2
496	IV.B.2		Perhaps the glossary should define primary stability batch	It might be argued that if the process changes from the time the primary stability batches were manufactured, those batches now become supportive stability batches	3
500	IV.B.2		Only adequately defined 'critical process controls' should have to be reported	Rid NDA of detail that is not critical to quality	1
510-11	IV.B.2		Environmental controls should only be included if non-standard conditions are critical to the process		2
519	IV.B.2		Steps in the process should have the appropriate **critical** process controls identified	Not all controls need be reported	
521	IV.B.2		All critical process controls, ~~critical or otherwise,~~ should be included . .	Rid NDA of detail that is not critical to quality	1
538	IV.B 2		All of the operating parameters, environmental conditions, and process tests that are critical to ensuring each critical manufacturing step is properly controlled should be specifically identified	Consistent with earlier arguments	1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
547	IV.B.3		The word 'Critical" should be added to each box in the third tier of this figure	Consistent with earlier arguments	1
557	IV.B.3		Information (e.g., comparative analytical data) to support the appropriateness of ~~these~~ reworking operations should be included	Reprocessing should not need to be addressed in the NDA	2
565	IV.B.3.a		The discussion of reprocessing fails to address the combining of partial lots post-release, as long as each lot is still within specifications.	This is common industry practice and should be provided for.	1
578	IV.B.3.a		Repetition of multiple chemical reaction steps, but not multiple unit operations, . . .	For clarification	3
581	IV.B.3.a		The statement that reprocessing need not be described in the application should be moved up front in this discussion.	This is an important point to a discussion of NDA/MF content and should be made more visible	3
605	IV.B.3.b		Repetition of multiple chemical reaction steps, but not multiple unit operations, . . .	For clarification	3
622	IV.B.3.c		~~The use of recovered solvents and~~ recycling of filtrates (mother liquors) to recover reactants, intermediates, or drugs substance	If recovered solvents are returned to virgin condition, no reporting should be required	2
628	IV.B.3.c		This paragraph should be deleted and replaced with: The use of solvents which are not returned to virgin specifications must be demonstrated to be suitable for use and this documentation maintained by the manufacturer	The information requested in the referenced paragraph would add to regulatory burden, discourage reuse of solvents and increase ecological burden	2

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
630	IV.B.3.c		~~The use of recovered solvents, including the point at which they might be used in the process, should be included in the description of the manufacturing process.~~	This is not important information to control of the drug substance	2
655	IV.B.3 e		This section deals with reprocess/rework and should be included with sections IV.B.3.a. and b.	Seems misplaced in current location	3
658	IV.B.3 e		a drug substance, after it has been released by the quality control department, that undergoes processing to bring the material back into conformance with its purity or potency specification ~~(e.g., purification of aged material to decrease the level of degradation products to conform with the approved acceptance criteria).~~	It may not be uncommon to recrystallize released material to remove newly detected extraneous material. This should be allowed under reprocessing.	2
698	IV.C.1		A proposed starting material for a synthetic drug substance should be chosen so that sufficient information will be available to FDA on the drug substance manufacturing process to evaluate its ~~the~~ safety and quality ~~of the drug substance.~~	To avoid possible confusion that FDA is requesting information on the starting material manufacturing process	3
713	IV.C.1		A flow diagram for the drug substance synthesis	For clarification that a flow diagram for the starting material is not required.	3
769	IV.D.		Only critical parameters and tests should need to be reported.	A separate list of non-critical tests adds no value.	1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
779	IV.D.		For all critical process controls, the associated numeric ranges, limits, or acceptance criteria should be defined ~~justified~~ and a brief description of the test provided.	A 'justification' of each critical test or control in the NDA would add to regulatory burden. These should be available for inspection at the manufacturing site	1
780-1	IV.D.		**Adequate** ~~Any~~ experimental data to support . . .	The term 'any experimental data' could be misconstrued to mean 'all experimental data,' which could be thousands of pages.	3
785	IV.D.		~~Critical process control values from relevant batches (i.e., those for which batch analyses have been provided in S.4.4) should be provided as part of the justification.~~	A 'justification' of each critical test or control in the NDA would add to regulatory burden. These should be available for inspection at the manufacturing site	1
886	IV.E.		when the reprocessing or reworking operations have a significant potential to adversely affect the identity, strength, quality, purity, or potency of the product (e.g., naturally derived protein drug substances). It is generally understood that many such situations will occur post-approval.	For clarification	3
1051	V.B.		Identity of the impurity or potential impurity (chemical name and structure or code)	For clarification	3
1059	V.B.		This bullet point should be deleted.	The synthesis of impurities is not generally required currently. Adequate characterization data should be provided for each impurity, but not the synthesis	2
1229	VI.C.		This information should be provided for all applicable analytical procedures listed in the specification (S.4.1).	Not all tests require validation, e.g., loss on drying	2

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
1241	VI.D.		~~Batch analysis reports (e.g., certificates of analysis (COAs))~~ Tabulations of batch results should be provided	This reflects current practice	2
1263	VI.D.1		The batch analysis reports, if provided, should include all specification tests . . . ~~Including tests that are not part of the proposed specification.~~	Tests that are not critical to control of drug substance quality should not be reported.	2
1267	VI.D.1		A summary of any **significant** changes . . .	Not all minor changes need be reported	3
1409	VIII		Delete requirements to submit specifications for primary and secondary packaging components	Currently, a discussion and description of the packaging has been included, but not the component specifications and the need to add this is requirement seems unwarranted.	2
1433	IX.A.		conclusions regarding the shipping and label storage conditions and retest or expiration dating period, as appropriate	Shipping conditions may be crucial to material quality	3
1451	IX.C.1		The meaning of the term 'intermediate studies' is not clear	For clarification	3
1488	IX.C.3		It would seem reasonable to include a summary of degradation pathways and structures based on stress studies and include precautions re. storage and handling	Information which has 'added value'	2
1518	X.A.		It would seem that this section might be handled in separate guidance.	Seems more applicable to biologics than drugs	3
1530	X.A.		It would seem that this section might be handled in separate guidance.	Seems more applicable to biologics than drugs	3
1553	X.A.		It would seem that this section might be handled in separate guidance.	Seems more applicable to biologics than drugs	3

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
1588	X.B.1		Certifications and/or documentation ~~certificates~~ relating to the safe use of bovine-derived materials should be provided, as appropriate. Current requirements include certification that bovine-derived materials are not sourced ~~and sourcing of materials~~ from BSE countries as defined by the U.S. Department of Agriculture (9 CFR 94.11)	Requirements are expected to change continually on this issue, and guidance here should be kept general and cross-reference up-to-date and specific requirements provided elsewhere.	2
1630	XI.A.		The terms 'executed batch record' and 'executed production record' should be harmonized, or the distinction clarified.	For clarification.	3
1683	Att. 1		A drug substance that is used to synthesize another drug substance is generally not an appropriate candidate for designation as a starting material	Starting materials have been approved which are drug substances, e.g., 5-fluorouracil, so exceptions have been allowed	1
1696	Att. 1		The starting material criterion of 'significant non-pharmaceutical market' is objectionable, and should be replaced with 'significant commercial market'.	There are many well characterized and commonly available starting materials which are produced only for the pharmaceutical sector, such as protected amino acids, functionalized sugars, functionalized purine bases, etc. There should be no difference in the assignment of these as opposed to those materials produced for, say, the foods sector, or the chemical sector.	1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
1708	Att. 1		Besides challenging the concept of 'significant nonpharmaceutical market,' these four criteria are questionable	(1) It is unclear whether 'to manufacture drug substance' refers to the subject drug substance, or any drug substance; (2) and (3) The significance of Phase 1 and 2 experience is unclear, especially if commercial availability has changed since those studies were conducted.	1
1740	Att. 1.I A.		The section on propinquity provides very little tangible guidance for manufactures.	'Several steps' will continue to be interpreted differently reviewer by reviewer. What is crucial is the level of quality improvement per step or unit operation and not the number of steps.	1
1742	Att. 1.I A.		should be separated from the final intermediate by ~~several~~ at least one-reaction steps	The term 'several' lacks clarity, but 'at least one' is somewhat better.	1
1744-51	Att.1.I A.		It is not very important, with regard to control of quality, how many steps separate a starting material from a final intermediate. Rather the efficiency of esach step in removing impurities is a more important focus of process control		1
1753	Att. 1.I A.		The focus on numbers of steps and what constitutes a step must be changed to a comprehensive discussion of the quality improvement and control as the end of the synthesis is approached.	The guidance should rely on sound scientific process and discussions, and not on arbitrary and subjective numbers of steps	1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
1764	Att. 1.I.A.		Solvent removal may be the means to provide a desired physical form, though purification is not actually taking place.		1
1777	Att. 1.I C.		This paragraph should be deleted.	This restriction on the source of impurities lacks scientific basis. Impurities in drug substance are qualified by safety data, regardless of their source.	1
1788	Att. 1.I C.		Delete these three bullets	The logic in these three points is unclear	2
1801	Att. 1.I D.		This paragraph on 'complexity' is far too vague and fails to provide meaningful guidance.	'Complex' is subjective. Many complex materials are very well characterized. The emphasis, thus, should be on the degree of characterization, not on perceived complexity.	1
1807-9	Att. 1,I.D.		This section is vague and subjective. "Limited" is not defined. Many compounds with multiple functionality can be and are well characterized and distinguishable. Again, the focus should be on characterization.		1
1811	Att. 1.I D.		The simple techniques cited in this first sentence should not be used to define 'complex.' This last sentence ignores the value in current analytical technology in the control of drug substance quality.	Most of the techniques cited in this section are in fact, quite simplistic, common and routinely available and must be allowed to be included in the control of starting materials. Characterization, not complexity, is the pertinent issue.	1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
1834	Att. 1.II.B.		~~Each synthesis branch should begin with chemicals that have a significant nonpharmaceutical market~~ . . .	A consistent definition of starting material must be applied. If a chemical does not have a significant nonpharmaceutical market but is the designated starting material, then this is where reporting is to begin.	1
1850	Att. 1.II.C.		Identification tests for a proposed starting material should be specific and should be able to discriminate between it and any likely related compounds ~~that are likely to be present~~.	This is a discussion of an identity test, not a purity assay	2
1863	Att. 1.II.C.		Remove point (1)	A starting material which is the first isolated and purified chemical counting backwards from the drug substance sounds inconsistent with the 'propinquity' criteria. The point seems adequately made in (2).	2
1873	Att. 1.II.D.		Again, the reliance on 'significant nonpharmaceutical market' must be avoided.	The differentiation between pharmaceutical and nonpharmaceutical markets as it relates to risk to quality assurance is unclear.	1
1876	Att. 1.II.D.		It is not at all clear how a sponsor would document the sales and marketing of a chemical vendor.	This seems to be an unrealistic requirement	2
1883	Att. 1.II.D.		Again, what is the value in differentiating the markets?	If there is any value in differentiating, one could argue that a significant pharmaceutical market is more critical to quality assurance	1
1884	Att. 1.II.D.		Examples of manufacturers who are able to provide quantities suitable **for commercial production.**		1

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
1924	Att. 1.II.D.2.c.		~~For each of the listed impurities, information should be provided to demonstrate that the impurity did not originate from the proposed starting material.~~	This point has been addressed under Line 1777 above. The provisions of this section as-is will add considerable regulatory burden and additional cost to the manufactuer (and consumer)	1
1984	Att. 1. III		Delete this paragraph.	It is not considered practical for drug substance manufacturers and starting material suppliers to maintain this kind of communication.	2
2122	Glossary		This definition of 'critical' lacks sufficient clarity to be useful for a sponsor.	This seems to be a more appropriate general definition for an 'in-process control' but not for what actually constitutes 'critical.'	2
2211	Glossary		The term 'then used immediately' should be deleted and a provision for establishment of subsequent retest dates must be provided	It has been common industry practice to establish subsequent retest dates based on sound scientific data. This practice must not be prohibited by a definition which fails to allow for flexibility based on good sound science.	1